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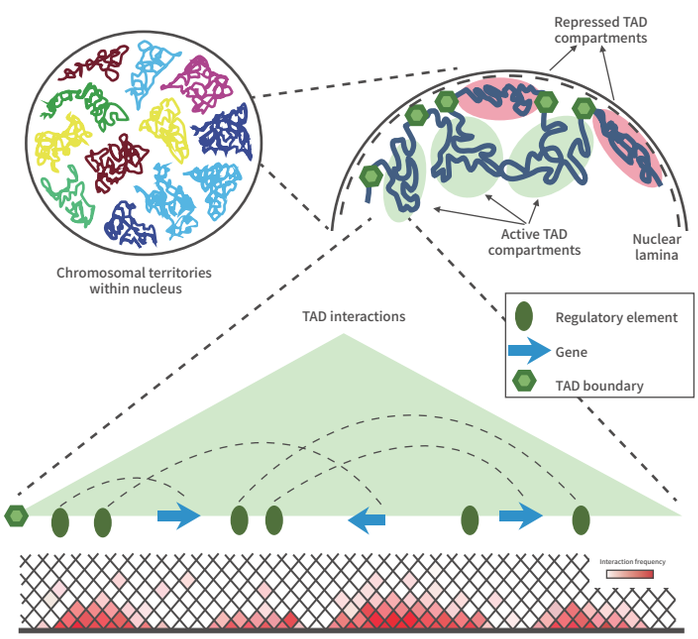
Hi-C—Technology for the 3D Genome Era

Case study：Genome-Wide Chromatin Structure Changes During Adipogenesis and Myogenesis

Background

High-throughput chromatin conformation capture (Hi-C) technology is derived from chromosome conformation capture (3C). Combined with NGS technology, it enables us to explore the spatial interaction between different gene loci throughout the genome and study DNA elements that regulate genes expression in three-dimensions(3D).

Adipose tissue and skeletal muscle tissue are two important organs involved in energy metabolism and physical movement. Their differentiation are regulated by complex molecular networks and epigenetic modifications. This study comprehensively mapped the 3D chromatin organization for four cell types to investigate the changes in the 3D chromatin structure and its mediated gene expression during adipogenesis and myogenesis.



Research Pipeline

Samples

4 cell types: 3T3-L1 pre-adipocytes and 3T3-L1-D adipocytes for adipogenesis; C2C12 myoblasts and C2C12-D myotubes for myogenesis

Library preparation

Hi-C library and RNA-seq library

Sequencing

Illumina platforms

Bioinformatics analysis

- Generation of interchromosomal interaction matrices
- Identification of compartment A (active chromatin regions) and B (inactive chromatin regions)
- Identification of topologically associating domains (TADs) and topological boundaries
- Identification of differential chromatin interactions
- Analysis of putative promoter–enhancer interactions
- Histone modification and chromatin accessibility
- Gene expression analysis
- Functional enrichment analysis

Research Result

1 Similar trans interactions occurred in nuclei across cell types and global conservation and divergence of cis interactions occurred during adipogenesis and myogenesis.

Adipogenesis and Myogenesis models were established and tested by morphology. ~332.40 M unique Hi-C read pairs were kept as authentic interactions. Among these, cis interactions are the dominant chromatin contacts (Fig.1 A). The normalized intrachromosomal interaction maps, at 1-Mb resolution, visually present the reproducible "plaid" patterns. These represent alternating regions with high and low interaction frequencies (Fig.1 B).

2 Extensive compartment A/B changes occurred during adipogenic and myogenic differentiation.

Compartments A and B represent the relatively active and inactive chromatin regions, respectively. Dynamic compartmentalization was observed during cell differentiation and between cell types (Fig.2).

3 Domain-level chromatin dynamics corresponded to cell differentiation.

The adipogenic marker gene, Fabp4-located TAD, was split into three in adipocytes with significantly upregulated gene expression (Fig.3).

4 Putative promoter interactions were involved in adipogenesis and myogenesis.

Increased local interactions of these putative promoters may contribute to adipogenesis and myogenesis by activating the expression of pro-differentiation genes (Fig.4).

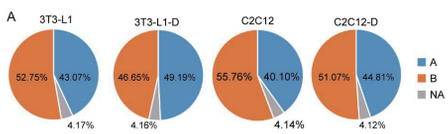


Fig. 2 Compartment A/B changes correlated with gene expression changes.

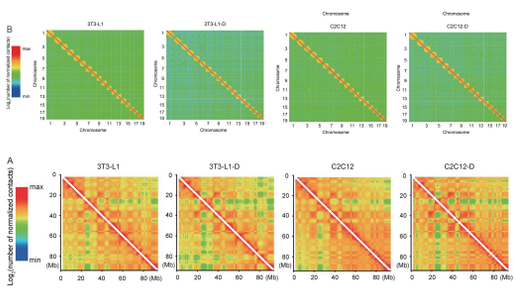


Fig. 1 A. Genome-wide chromatin interaction maps of four cell types; B. Reproducible "plaid" pattern of intrachromosomal interactions in four cell types.

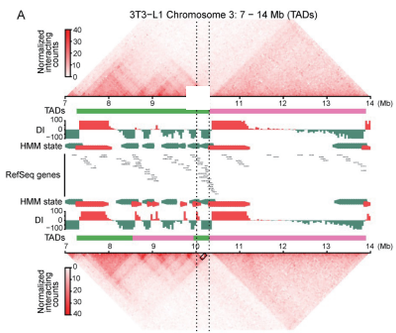


Fig. 3 Adipogenic differentiation generated adipocyte-specific chromatin interactions and correlated with gene activity

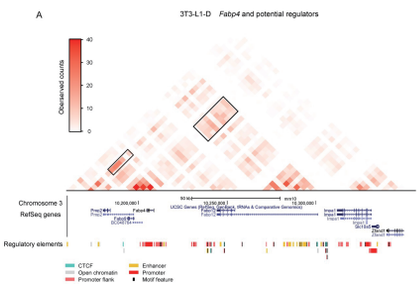


Fig. 4 Potential regulators of adipogenesis

Conclusion

The results provided evidence for further study of promoter-anchored chromatin loops to obtain a comprehensive understanding of the molecular regulatory mechanisms of adipogenesis and myogenesis.

Reference

He M, Li Y, Tang Q, et al. Genome-Wide Chromatin Structure Changes During Adipogenesis and Myogenesis[J]. International Journal of Biological Sciences, 2018, 14(11): 1571-1585.(PMID: 30263009)

Other Novogene Powered Literature

Year	Journal	Title
2018	Nature plants	Evolutionary dynamics of 3D genome architecture following polyploidization in cotton
2017	Cell	Cohesin Loss Eliminates All Loop Domains
2017	Cell	3D Chromatin Structures of Mature Gametes and Structural Reprogramming during Mammalian Embryogenesis